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Cleavage of Pyridine-Type Rings

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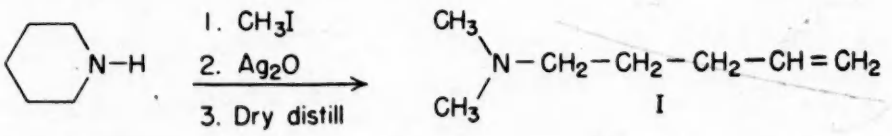
Pyridine, the most common six-membered mononitrogen heterocycle, is itself quite resistant to ring cleavage. Destruction of the aromaticity of the pyridine ring by reduction or by the formation of pyridinium salts through reaction of the unshared electron pair of the nitrogen with certain strong electron-attracting groups facilitates the opening of the pyridine ring.

Reactions Involving Pyridine Ring Cleavage during Reduction

It has been reported (1) that catalytic reduction of pyridine with nickel-type catalysts at elevated temperatures gives *n*-amylamine, *n*-pentane, and ammonia. Presumably, these products arise by the hydrogenolysis of the piperidine formed. Hydriodic acid treatment (2) of pyridine in a sealed tube at 300° C yields *n*-pentane and ammonium iodide. Reduction of pyridine with sodium and 95% ethyl alcohol (3) produces only a small amount of piperidine, the major product being a non-distillable polymer or glutaconaldehyde (III, see below) (isolated as the dioxime), depending on how the reaction is carried out. Good yields of piperidine are produced by this reduction, if absolute ethyl alcohol is used in place of 95% ethyl alcohol. Reduction of 2-picoline and some of its derivatives (4) forms cyclohexenone derivatives in yields of 12 to 30% by a series of steps involving reduction with sodium and alcohol in liquid ammonia, ammonolysis, and ring closure.

Reactions Involving Piperidine Ring Cleavage

A reaction which is of very limited value in organic synthesis, but a valuable tool in the structure determination of some alkaloids is the exhaustive methylation reaction. Piperidine (5) is cleaved by this reaction to form 5-dimethylamino-1-pentene (I), according to the following scheme:



Further treatment of (I) produces piperylene and treatment of (I) with hydrochloric acid, followed by sodium hydroxide, produces 1,2-dimethylpyrrolidine. A similar cleavage of piperidine (6) occurs when 1,1-dimethylpiperidinium chloride is treated with hot sodium hydroxide to yield 5-dimethylamino-1-pentene (I). 1-Alkyl- and 1-aryl-piperidines react with cyanogen bromide or chloride to form

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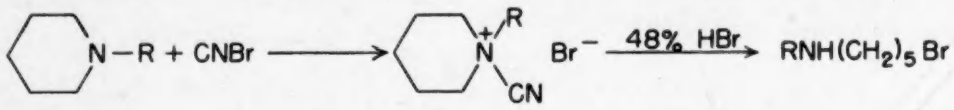
quaternary compounds which hydrolyze with the opening of the piperidine ring (7). The reaction proceeds in the following manner when R is phenyl:



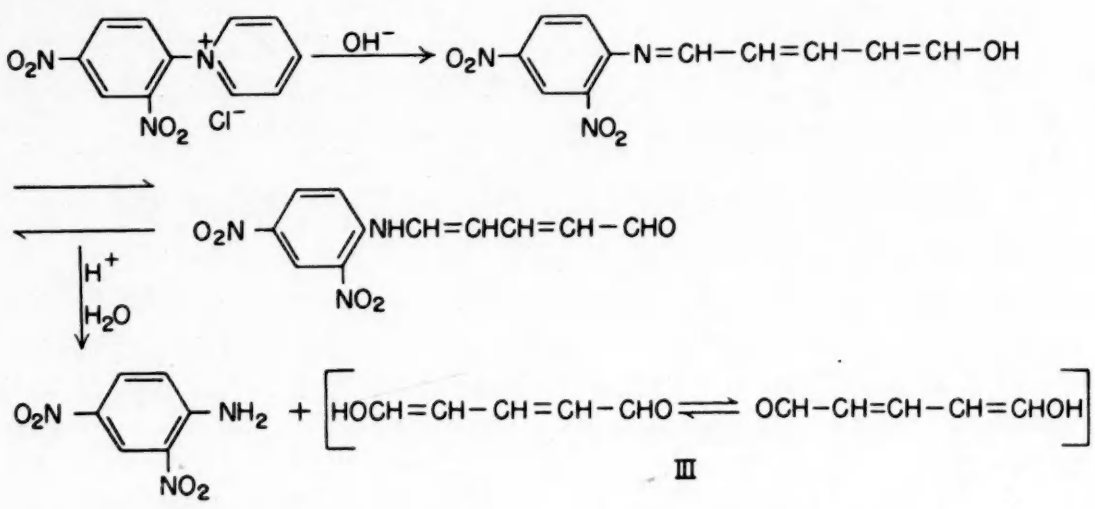
II

Another reaction, namely, that of eliminating RBr, becomes progressively more important as the R group is changed from phenyl to isopropyl, propyl, ethyl, methyl, benzyl, and allyl. The action of phosphorus pentachloride on 1-benzoylpiperidine results in a smooth cleavage of the piperidine ring (8). Thus, 1,5-dichloropentane and ϵ-benzoylaminoamyl chloride have been prepared in good yields. Use of phosphorus pentabromide affords a method (9) of preparing 1,5-dibromopentane in 70% yield. Piperidine is also susceptible to the action of oxidizing agents. Hydrogen peroxide and piperidine (10) give ϵ-aminovaleraldehyde, and potassium permanganate opens 1-benzoylpiperidine to form δ-aminovaleric acid (11).

Reactions Involving Hydrolysis of Pyridinium Compounds

The number of pyridinium salts which hydrolyze with a cleavage of the pyridine ring is too large for a detailed discussion here (12). The following compounds are some of those more frequently studied which do form quaternary salts that hydrolyze quite readily: 1-chloro-2,4-dinitrobenzene, 4-chloropyridine, cyanogen bromide, chlorosulfonic acid, sulfur trioxide, phosphorus pentachloride, phosphorus oxychloride, and phosgene.

The reaction of 2,4-dinitrophenylpyridinium chloride with various bases to open the pyridine nucleus probably has been the one most thoroughly studied. The quaternary salt is obtained in an 89% yield when pyridine and 1-chloro-2,4-dinitrobenzene are heated together on a steam-bath (13). The product, 2,4-dinitrophenylpyridinium chloride (II), reacts readily with various primary and secondary amines, and alkaline inorganic compounds such as sodium hydroxide, sodium carbonate, and sodium acetate (14).



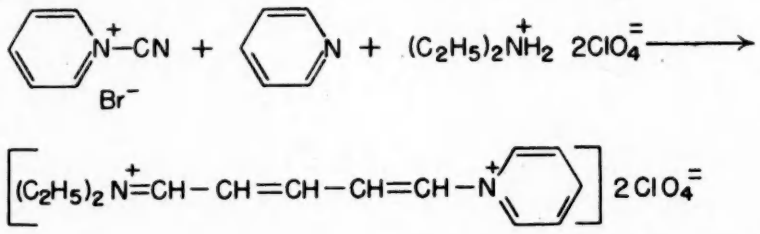
III

Glutaconaldehyde (III) has not been isolated in the free state but exists in solution, and can be isolated from the above reaction in a 70% yield in the form of its dianil. Recently (15), the influence of substituents in the 3- or 4-position of the pyridine ring on this reaction has been studied. It was found that 3-methyl-, 3-hydroxy-, 3-methoxy-, 3-acetamido-, 3-dimethylamino-, 3-iodo-, 3-diethylcarbamyl-, 4-acetamido-, and 4-phenylaminopyridine all form the expected quaternary compound with 1-chloro-2,4-dinitrobenzene; however, no addition was found with

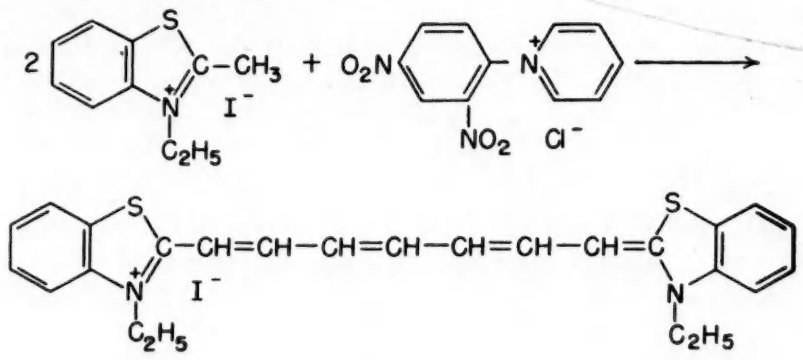
3-chloro-, 3-bromo-, 3-nitro-, and 3-carbethoxypyridine, and very little with 4-carbethoxypyridine. Weak electropositive groups (methyl, methoxy, and acetamido) in the 3-position of pyridine cause the yield of cleavage product to be lower when the quaternary salt is reacted with aromatic bases, such as aniline, at 0 to 10 C, than with pyridine itself. Strong electropositive groups prevent ring cleavage entirely. Another series of compounds has been prepared by these workers in which the pyridine ring is substituted in the 4-position by an alkoxy group containing 1-5 carbon atoms. Above 50 C, 4-methoxypyridine gives two reactions when reacted with 1-chloro-2,4-dinitrobenzene. One product is the expected pyridinium salt, and the other is 1-(2,4-dinitrophenyl)-4(1H)-pyridone which is formed by elimination of methyl chloride from the quaternary compound. The higher 4-alkoxy homologues react in a manner similar to the methoxy compound at temperatures of 100 to 150 C. It was also found that 4-hydroxypyridine reacts, upon contact with 1-chloro-2,4-dinitrobenzene, to yield the pyridone by the loss of hydrogen chloride. Treatment of 1-(2,4-dinitrophenyl)-4-methoxypyridinium chloride with aniline gives, instead of the expected cleavage product, the compound, 1-(2,4-dinitrophenyl-4-anilinopyridinium chloride.

If thionyl chloride is reacted with pyridine for three days at room temperature or for five hours on a steam-bath, the salt 1-(4-pyridyl)-pyridinium chloride hydrochloride (IV) is formed in fair yields (16). This compound reacts with bases in a manner similar to 1-(2,4-dinitrophenyl)-pyridinium chloride to open the pyridine ring and produce the monoanil of glutaconaldehyde and 4-aminopyridine.

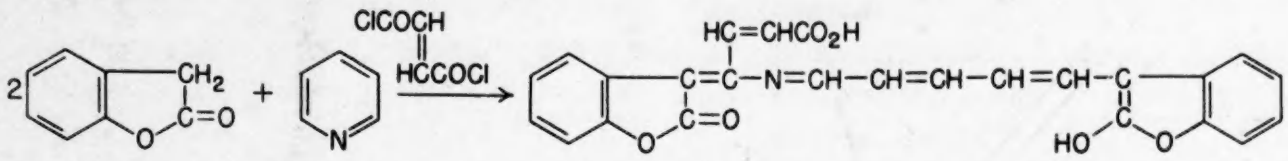
Koenigs and Greiner (16) report that (IV) gives a 75% yield of 4-hydroxypyridine, upon hydrolysis with water in an autoclave at 150 C for eight hours, and a 60% yield of 4-aminopyridine under the same conditions with ammonia. Glutaconaldehyde (III) can be isolated in a 60% yield as its dianil from these reactions. Hydrolysis of (IV) with aniline produces 4-phenylaminopyridine, and 4-phenoxypyridine is formed when potassium phenoxide is used. An interesting reaction has been reported (17) based upon the opening of 1-cyanopyridinium bromide.



1-Diethylimidonium-5-pyridinium-glutacondialdehyde diperchlorate (V) may then be treated with aniline, diethylamine, water, or sodium hydroxide to form other compounds having a high degree of unsaturation. 1-Cyanopyridinium bromide (18) and 1-(2,4-dinitrophenyl)-pyridinium chloride (13) have been used for preparing other polymethine compounds. Fisher and Hamer (13) prepared a polymethine cyanine type dye in the following manner:



A recent paper (19) reports other highly conjugated compounds which are prepared by the opening of the pyridine ring. The preparation of some of these compounds may be illustrated as follows:



Benzoylchloride reacts in a similar manner. 1-chloro-2,4-dinitrobenzene reacts with these reagents to form 3-[5-(2,4-dinitrophenylimino)-1,3-pentadienyl]-2-benzofuranal.

Pyridine reacts with three moles of sodium bisulfite to form a white solid which reacts with strong bases (20) to form ammonia, water, sodium sulfite, and glutaconaldehyde (III). After standing for several months, β-vinylacrylic acid has been isolated from a mixture of pyridine, chloroform, and sodium hydroxide (21). Bromoform, iodoform, carbon tetrachloride, benzotrichloride, and trichloroacetic acid all react in the same manner as chloroform. Freytag (22) has reported that the color which develops in pyridine upon exposure to light is due to a ring cleavage of the pyridine ring. He terms the coloring material "photopyridine" and he has shown it to be the ammonium salt of glutaconaldehyde (III). This compound is apparently formed by a reaction of hygroscopically adsorbed water with pyridine to form pyridinium hydroxide, which reacts with another molecule of water, in which case the water acts as a base and cleaves the ring.

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